ORIGINAL ARTICLE

Bali Medical Journal (*Bali Med J*) 2019, Volume 8, Number 2: 496-500
P-ISSN.2089-1180, E-ISSN.2302-2914

Published by DiscoverSys

Hemostasis changes and its relationship with SOFA score in sepsis patients

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ABSTRACT

Introduction: Sepsis is a major health problem, and the incidence is still increasing. Generally, sepsis occurs in about 2% of all inpatients in developed countries. The immunologic response that causes sepsis is a systemic inflammatory response that causes activation of the inflammatory and coagulation pathways. If sepsis untreated, it can lead to organ failure then death. Organ dysfunction is expressed as an acute change of Sequential Organ Failure Assesment (SOFA) score >2 points as a consequence of infection.

Methods: This is a cohort prospective's study. Prothrombin time (PT), activated partial thromboplastin time (aPTT), Thrombin time (TT), Fibrinogen, D-dimer were examined 3 times (first, second, third day), and then assessed to see its relation with the corresponding SOFA score. Twenty-four subjects of the study were ICU patients in H. Adam Malik Hospital who matched the inclusion and exclusion criteria.

Results: There were significant differences of PT on the first, second and third day ($p = 0.03$). There were no significant differences in aPTT, TT, Fibrinogen, D-dimer on the first, second, third day. There were no significant correlations of PT, aPTT, TT, Fibrinogen with the corresponding SOFA score on the first, second, third day. There was a moderate positive correlation between D-dimer and SOFA score in the first, second and third day of examinations ($p < 0.05$).

Conclusion: PT changes occurred significantly on the first, second, third day of sepsis and D-dimers can be used to asses the risk of organ failure in septic patients.

Key Word: aPTT, D-dimer, Fibrinogen, PT, Sepsis, SOFA Score, TT

Cite this Article: Giri, S.H.N., Aman, A.K., Hanafie, A. 2019. Hemostasis changes and its relationship with SOFA score in sepsis patients. *Bali Medical Journal* 8(2): 496-500. DOI:10.15562/bmj.v8i2.1409

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Received: 2018-12-01
Accepted: 2019-01-29
Published: 2019-08-01

INTRODUCTION

Sepsis is a life-threatening organ dysfunction due to an imbalance in the body's response to infection. If sepsis was not treated immediately, it can lead to failure of organ function and subsequently leads to death. The immunologic response that causes sepsis is a systemic inflammatory response that causes activation of the inflammatory pathway and coagulation.[1] The aspect of coagulation disorder from sepsis is the occurrence of an imbalance between the activation of coagulation and anticoagulation. More specifically, augmentation of pro-coagulation factors and depletion of anti-coagulation factors.[2] Organ dysfunction expressed as acute changes in total Sequential Organ Failure Assessment (SOFA) scores more than two points as the consequence of infection. SOFA values considered zero in patients without organ dysfunction. SOFA score more than two is associated with the higher risk of death."[1,3]

Sepsis is a major health problem, and its incidence continues to increase. In general, sepsis occurs in about 2% of all hospitalized patients in developed countries. Sepsis can occur between 6-30% of patient in intensive care units (ICUs), with considerable variation due to heterogeneity among ICUs.[4] In most developed countries, the incidence of severe sepsis has been estimated between 50-100 cases per 100,000 person in the general population. It is estimated that one-third to one-half of all sepsis patients will eventually die. In developing countries, sepsis accounts for 60-80% of all deaths. It kills more than six million babies and young children, and 100,000 new mothers every year. Every 3-4 seconds, someone in the world dies of sepsis.[5,6]10th Revision (ICD-10 Research conducted on patients with severe sepsis among 150 intensive care units (ICUs) in sixteen Asian countries found that the hospital mortality rate reached 44.5%.[7] In research at a teaching hospital in Yogyakarta, Indonesia, there were 631 cases of sepsis in 2007, with a mortality rate of 48.96%.[8]

Based on research conducted by Suliarni in 2002, it was shown that the extrinsic pathway was pivotal in the occurrence of clotting system disorders in sepsis. Furthermore, the most widely reported factor that plays an important role is the tissue factor. From the research conducted by Suliarni, which compared the levels of prothrombin time (PT) in sepsis patients and normal patients showed prolonged prothrombin time in sepsis patients.[9,10] Another studies conducted by Yessy *et al.* at Dr. Soetoemo Surabaya in 2016,

shown that D-dimer levels could also be used as a predictor for organ dysfunction in septic patients.[11]

Based on these previous studies, the researchers were interested in knowing the changes in hemostasis that occurred in septic patients and to investigate the relationship between changes in hemostasis and the SOFA score.

METHODS

This is a Cohort Prospective study to investigate the hemostasis changes in sepsis patients performed on three different measurement (first, second, and third days), and assessed its relationship with SOFA scores evaluated at the same day. The study conducted in the Clinical Pathology Department, Medical Faculty University of Sumatera Utara/Haji Adam Malik Central Public Hospital, in collaboration with the Department of Anesthesiology & Intensive care. The inclusion criteria were septic patients, aged 18-65 years and willing to take part in the study. Exclusion criteria were patients who had received anticoagulant therapy before the study, patients with chronic liver disease and hematological abnormalities before suffering from sepsis, patients who did not complete the clinical and laboratory examination and patients who returned home at their own/family request before the third examinations. Repeated ANOVA was used for data with normal distribution, and Friedman test for non-normal distribution. Whereas to assess the relationship of hemostasis changes to SOFA scores, Pearson correlation test was used for normal distributed data and Spearman rho correlation test for data with non-normal distribution. The analysis was carried out with 95% confidence intervals, and p-value less than 0.05 considered significant.

Table 1 Baseline Characteristics Sepsis Patients

Variable	n = 24
Age (years old) (Median Ranges)	53 (18-65)
Gender (%)	
Male	13 (54,2%)
Female	11 (45,8%)
Ethnicity (%)	
Batak	16 (66,7%)
Java	5 (20,8%)
Padang	1 (4,2%)
Melayu	1 (4,2%)
Karo	1 (4,2%)

RESULTS

The characteristics of the study subject in the form of age, gender, and ethnicity was presented in Table 1. In this study, there were 24 patiets with sepsis involved, composed of 13 men (54.2%) and 11 women (45.8%). The average age of sepsis patients was 53 years, with the oldest being 65 years and the youngest was 18 years. In this study, 16 people were Batak (66.7%), five Javanese (20.8%), one Padang (4.2%), one Malay (4.2%), and one Karo (4.2%).

There was a significant difference of mean Prothrombin time among the three measurements in repeated measure ANOVA ($p < 0.05$) as shown in table 2. There were no statistically significant changes in SOFA score on the first, second and third days. The relationship between prothrombin time and SOFA were analyzed with Pearson correlation. The relationship between prothrombin time compared to its corresponding SOFA score at each day, and the results were positively correlated but not statistically significant at all measurement.

Table 3 shows that the aPTT value did not show a significant difference among three measurements in Friedman test ($p > 0.05$). The table above also shows the result of Spearman rho correlation analysis between the aPTT and its corresponding SOFA score at each day. The results were positively correlated but not statistically significant at all measurement.

Table 4 shows that the TT value did not show a significant difference among three measurements in Friedman test ($p > 0.05$). The table shows the result of Pearson correlation analysis between the TT and its corresponding SOFA score at each day. The results were negatively correlated but not significant at first and second day. Results at third day showed positive correlation but also not statistically significant ($p = 0.95$).

Table 5 shows that the mean fibrinogen value did not show a significant difference among three measurements in Friedman test ($p > 0.05$). The table also shows the result of Pearson correlation analysis between the fibrinogen and its corresponding SOFA score at each day. The results were negatively correlated but not significant at all measurement.

Table 6 shows that the mean D-dimer value did not show a significant difference among three measurements in Friedman test ($p > 0.05$). The table shows the result of Pearson correlation analysis between the D-dimer and its corresponding SOFA score at each day. The result was a statistically significant positive correlation between D-dimer and its corresponding SOFA score at all measurement.

Table 2 The Mean of Prothrombin Time Level and Its Correlation with SOFA Score

Parameter	Day 1	Day 2	Day 3	*p-value*
PT (Mean ± SD)*	20,68 ± 22,59	22,30 ± 22,36	21,18 ± 22,69	0,03***
SOFA (Mean ± SD)*	5,04±2,53	4,38±2,68	4,29±3,26	0,60
r	0,41**	0,56**	0,46**	
p-value	0,608	0,961	0,607	

** Repeated ANOVA; ** Pearson Correlation; *** p-value* < 0.05 considered significant

Table 3 The Mean of Activated Partial Thromboplastin Time Level and Its Correlation with the SOFA Score

Parameter	Day 1	Day 2	Day 3	*p-value*
APTT(*Median ranges*)*	27,9 (18,7-45,5)	31,1 (19,8-42,0)	27,1 (20,1-37,5)	0,076
SOFA (Mean±SD)**	5,04±2,53	4,38±2,68	4,29±3,26	0,6
r	0,38***	-0,76***	-0,25***	
p-value	0,60	0,72	0,23	

** Friedman;** Spearman's rho;*** Repeated ANOVA;**** p-value*< 0.05 *considered significant*

Table 4 The Mean of Thrombin Time (TT) Level and Its Correlation with the SOFA Score

Parameter	Day 1	Day 2	Day 3	*p-value*
TT (*Median Ranges)**	14,8 (9,6-25,2)	17,0 (13,5-27,6)	17,5 (12,4-28,1)	0,96
SOFA (Mean±SD)**	5,04±2,53	4,38±2,68	4,29±3,26	0,60
r	-0,23***	-0,21***	0,12***	
p-value	0,27	0,30	0,95	

** Friedman;** Spearman's rho;*** Repeated ANOVA;**** p-value*< 0.05 *considered significant*

Table 5 The Mean of Fibrinogen Level and Its Correlation with the SOFA Score

Parameter	Day 1	Day 2	Day 3	*p-value*
Fibrinogen (*Median Ranges)**	426 (135-900)	351 (234-900)	330 (118-900)	0,074
SOFA (Mean±SD)**	5,04±2,53	4,38±2,68	4,29±3,26	0,60
r	-0,28***	-0,20***	-0,27***	
p-value	0,17	0,32	0,18	

** Friedman;** Spearman's rho;*** Repeated ANOVA;**** p-value*< 0.05 *considered significant*

Tabel 6 The Mean of D-dimer and Its Correlation with the SOFA Score

Parameter	Day 1	Day 2	Day 3	*p-value*
D-dimer (*Median Ranges)**	1473 (89-5911)	1484 (100-5812)	1320 (119-4598)	0,10
SOFA (Mean±SD)**	5,04±2,53	4,38±2,68	4,29±3,26	0,60
r	0,41***	0,56***	0,46***	
p-value	0,04****	0,004****	0,02****	

** Friedman;** Spearman's rho;*** Repeated Anova;**** p-value*< 0.05 *considered significant*

DISCUSSION

In this study, there were twenty-four people with sepsis, 13 men (54.2%) and 11 women (45.8%). Previous research conducted by Yessica Putri *et al.* in 2014 found that sex was significantly associated with sepsis (p <0.05), adult male was 2.562 times more susceptible to sepsis compared with female adult.[12] This finding was consistent with the study conducted by Melamed *et al.*, which states that women were less likely to experience death related to sepsis than men in all racial/ethnic groups.[13] In the

Published by DiscoverSys | *Bali Med J* 2019; 8(2): 496-500 | doi: 10.15562/bmj.v8i2.1409

study by Angele *et al*., female sex steroids produce substances that thought to have immunoprotective effect in the event of trauma or bleeding.[12,14]

The average age of septic patients in this study is 48 years, with the oldest age being 65 years old and the youngest age being 18 years old. Previous research at dr. Kariadi Public Hospital, showed that mean age of patients with sepsis was 49.29 ± 17,399 years old.[12,15] Based on recent epidemiological studies from North America found that about 3 cases of sepsis per 1000 populations, which are interpreted into an annual estimate of around 700,000 - 750,000 cases per year. The overall mortality rate is around 30%, and it increases as the age gets older. This high incidence of sepsis was partly caused by increased elderly patients with chronic diseases.[16]

Suliarni *et al*., in their study in 2002, showed that it turned out the extrinsic pathway was pivotal for the occurrence of clotting system disorders in sepsis. Furthermore, the most widely reported factor plays the main role was tissue factor. Suliarni *et al*., compared the levels of prothrombin time and found that the prothrombin time was significantly prolonged in septic patients compared to normal patients. A similar result also produced in this study, there was a change in prothrombin time in sepsis patients when measured on the first, second, and third days, and when compared with normal values, sepsis patients showed prolonged the prothrombin time. This is in accordance with the theory, which states that tissue factors are the initial coagulation activators through extrinsic pathways and the most important main activator in sepsis pathogenesis. Extrinsic pathway involvement was indicated by abnormal PT.[9,10]

In this study, there were no significant increase in fibrinogen levels on the first, second and third days of sepsis. However when compared with normal reference values, there has been an increase in fibrinogen levels in the sepsis patients. This is in accordance with the theory, which states that fibrinogen levels can increase at the beginning of sepsis because the nature of fibrinogen as an acute phase reactant is released at the time of infection and the levels are still increasing for an extended time.[17]

In this study, it was found that there was also no significant difference of D-dimers among measurement in the first three days. Although when compared to normal values, sepsis patients showed increased amount of D-dimers in the circulation. This is in accordance with the theory, which states that D-dimer levels are increased in most septic patients due to coagulation activation that will soon be followed by activation of fibrinolysis. In the process of fibrinolysis, cross-linked fibrin will be broken down by plasmin to produce D-dimers so that the level of D-dimer will increase in circulation.[18]

In a previous study conducted by Yessy *et al*. at Dr. Soetoemo Hospital Surabaya in 2016, shown that D-dimer levels could be used as a predictor for organ dysfunction in septic patients. There was a significant positive correlation ($r = 0.580$, $p = 0.01$) between D-dimer and couch score.[11] D-dimer increased significantly according to the severity of sepsis. Previously Philip *et al*. in 2010 used D-dimer of 100 sepsis patients to predict which patients would have a SOFA score greater than 3 (three) during the first 48 hours. The study result shown a sensitivity of 93% (95% CI 72-99) and a specificity of 15% (95% CI 12-16).[19] Our study also point to same result as the levels of d-dimer have a positive and significant correlation with SOFA scores.

CONCLUSIONS

The results of this study indicate that prothrombin time changed significantly on the first, second and third days of sepsis while there was no significant changes of activated partial thromboplastin time, thrombin time, fibrinogen, and D-dimer. This study also showed increased levels of fibrinogen and D-dimer on the first, second, and third days of sepsis, when referred to normal values. Whereas D-dimer showed positive and significant correlation with SOFA score that it is expected to be used as a predictor for organ failure. A larger number of samples and longer time spans are needed for further research. This study is intended to help clinicians in providing therapy and preventing complications of organ dysfunction in septic patients.

ETHICAL CLEARANCE

This research has received ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara (No. 554/TGL/KEPK FUSU-RSUP HAM/2018), and also from Health Research Ethics Committee in Haji Adam Malik General Hospital (No. 345/UN5.2.1.1.1.9/PPM/2018).

CONFLICT OF INTEREST

All of the authors have no conflict of interest to disclose.

FUNDING

The funding support was received from PT. Setia Anugrah Medika.

AUTHOR'S CONTRIBUTION

Sarah Hanna Nadya Giri contributes to the main idea, wrote out the manuscript and revised the final manuscript. Sarah Hanna Nadya Giri, Adi Koesoema Aman, and Achsanuddin Hanafie together discussed the study design, collected the clinical and laboratory data, analyzed and interpreted all of the results. Sarah Hanna Nadya Giri together with Adi Koesoema Aman did the laboratory test, whereas Achsanuddin Hanafie were in charge of the sampling process.

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